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REMARKS

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Oath/Declaration

The oath or declaration has been objected to as defective because the Combined Declaration and Power of Attorney submitted February 17, 1998 does not identify that the instant application is a continuation-in-part of 08/702,205. A replacement Combined Declaration and Power of Attorney has been submitted herewith listing the application numbers of the applications to which the instant application claims priority. The Applicant respectfully requests that the objection to the oath or declaration be withdrawn.

The 35 U.S.C. §103(a) Rejection

Claims 8-15 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Tanimoto *et al.* (*Leukemia*, 3:339-348, 1989) or Scheinberg *et al.* (*Leukemia*, 3:440-445, 1989) in view of Thorpe *et al.* (*Immunological Reviews*, 62:119-158, 1982), Andrews *et al.* (*Blood*, 62:124-132, 1983) and Rosenblum *et al.* (U.S. Patent No. 5,631,348, Filed August 14, 1990). These rejections are respectfully traversed.

Tanimoto et al. and **Scheinberg et al.** teach an anti-CD33 monoclonal antibody M195. **Thorpe et al.** teach conjugation of antibodies to gelonin. **Andrews et al.** teach anti-CD33 antibodies may be useful for the treatment of leukemia. **Rosenblum et al.** teach the sequence of gelonin. Nevertheless, Applicant respectfully submits that combining these references does not lead to the claimed invention, nor do they encompass all the important features of the present invention.

Although the references teach M195 and gelonin, they do not specifically teach M195 conjugated to recombinant gelonin. **Tanimoto et al.**, **Scheinberg et al.** (Leukemia, 3:440-445, 1989), **Thorpe et al.** and **Andrews et al.** do not teach or suggest the making and using of M195 conjugated to recombinant gelonin, whereas **Rosenblum et al.** do not teach or suggest conjugating recombinant gelonin to M195 for cancer treatment. While the above combination of references might suggest that it would be obvious to try to conjugate M195 to gelonin to form an effective immunotoxin, one skilled in the art would have no method of knowing beforehand a functional immunotoxin would result from

such a conjugation. It is possible that the conjugation event could either alter the binding site of the antibody or reduce the toxicity of the gelonin conjugate. Further time-consuming, non-routine experimentation would be necessary to show that a functional immunotoxin was produced.

In addition, for immunotoxins to be effective, they must be effectively internalized into the target cell, and they must be directed to the correct intracellular compartment in order for the toxin to kill the cell. For example, uptake of the toxin into the lysosomal compartments may lead to the enzymatic digestion of the toxin before it can have any effect on the cell. Because the actual cytotoxicity of antibody-cytotoxin conjugates vary as a result of complex factors, it would not have been obvious beforehand that a functional immunotoxin would result from the conjugation of M195 to gelonin without additional, undue experimentation. In contrast, the present invention has detailed disclosure on the effectiveness of the M195-recombinant gelonin conjugate *in vitro* (Examples 9, 10) and *in vivo* (Example 14). Applicant also has evidence that indicate efficacy and lack of significant toxicity of the M195-recombinant gelonin conjugate in clinical setting.

The Applicant respectfully submits that no teaching, suggestion or incentive may be gleaned from the references, individually or together, with regard to the making and using of the claimed invention. Therefore, the invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicant respectfully requests that the rejection of claims 8-15 under 35 U.S.C. §103(a) as obvious over **Tanimoto** or **Scheinberg** (*Leukemia*, 3:440-445, 1989) in view of **Thorpe**, **Andrews** and **Rosenblum** be withdrawn.

Claims 8-15 remain rejected under 35 U.S.C. §103(a) as being unpatentable over **Scheinberg** (U.S. patent 5,730,982, March 24, 1998) in view of **Thorpe et al.** (*Immunological Reviews*, 62:119-158, 1982), **Andrews et al.** (*Blood*, 62:124-132, 1983) and **Rosenblum et al.** (U.S. Patent No. 5,631,348, Filed August 14, 1990). This rejection is respectfully traversed.

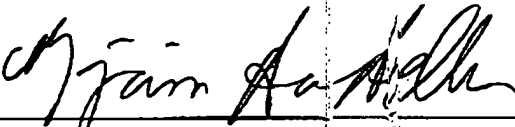
Thorpe et al., **Andrews et al.** and **Rosenblum et al.** have been discussed in detail above. U.S. patent 5,730,982, issued to **Scheinberg**, teaches the use of M195-radioisotopes conjugates

in cancer treatment. However, the cited patent does not teach, suggest or show data on the making and using of the M195-recombinant gelonin conjugate for cancer treatment. As with the combination of Thorpe *et al.*, Andrews *et al.* and Rosenblum *et al.* with Tanimoto or Scheinberg (*Leukemia*, 3:440-445, 1989), the combination of Thorpe *et al.*, Andrews *et al.* and Rosenblum *et al.* with Scheinberg (U.S. patent 5,730,982) provides no evidence that M195 conjugated to gelonin will result in an effective immunotoxin for cancer treatment. Once again, it is possible that the conjugation event could either alter the binding site of the antibody or reduce the toxicity of the gelonin conjugate or that problems may arise in the effective internalization of the conjugation into the target cells. While the combined references may suggest that it is obvious to try to form an effective immunotoxin by conjugating M195 to gelonin, additional, undue experimentation would be necessary to show that the formed immunotoxin was effective. Accordingly, Applicant respectfully requests that the rejection of claims 8-15 under 35 U.S.C. §103(a) as obvious over the combination of Scheinberg (U.S. patent 5,730,982) Thorpe, Andrews and Rosenblum be withdrawn.

This is intended to be a complete response to the Office Action mailed July 13, 2000. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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